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PRINCIPAL INVESTIGATOR: Eric Collisson

CONTRACTING ORGANIZATION: University of California, San Francisco
San Francisco, CA 94103

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) W. Michael Korn University of California, San Francisco 2340 Sutter St., Box 1387 San Francisco, CA 94158 Yelena Y Janjigian MSKCC 300 E66th St., Room 1003 New York, NY 10065 Eric Collisson University of California, San Francisco 1450 Third St. 375 Box 0128 San Francisco, CA 94158 Lawrence Fong University of California, San Francisco 513 Parnassus Ave 301A, Box 0519 San Francisco, CA 94143 Alan Ashworth University of California, San Francisco 1450 Third St. 271 Box 0128 San Francisco, CA 94158		8. PERFORMING ORGANIZATION REPORT NUMBER

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14. ABSTRACT <p>We performed the screen of gastric cancer cell lines for their sensitivity to small molecule inhibitors of PARP (rucaparib, talazoparib, olaparib, AZD2461) alone, or in combination with MEK inhibitors. We also generated a modified CRISPR system using dCas9-KRAB expressing variants of these cells, and validated them for CRISPRi screening. These reagents will next be used for a sensitization screen to PARPi, ATRi and MEKi treatment.</p> <p>In the drug response assays, cell lines differed dramatically in their sensitivity and resistance to these drugs. A subset of gastric cancer cells showed synergistic response to a combination of PARPi olaparib or talazoparib with MEK inhibitor GSK1120212 (trametinib), while the other cells were resistant to one or to both PARPi and MEKi. The predictive mechanism of cellular response is currently under study. We compared DNA damage signaling in gastric cancer cell lines. Pretreatment of cells with MEKi abolished activation of ATM and BRCA1 induced by either PARPi or the DNA-damaging agent Etoposide. Synergistic cell lines displayed downregulation of DNA damage-induced phospho-H2Ax and phospho-ATM when pretreated with MEKi. This effect was pronounced higher when the cells were pretreated with a combination of PARPi and MEKi.</p>				
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1. Introduction

A major risk factor for gastric cancer is infection with *H. pylori*. In addition, exposure to ionizing radiation as well as infection with Epstein-Barr Virus are associated with the disease. A common feature of these pathogens is DNA damage induction and activation of DNA damage response mechanisms. Germ-line as well as somatic mutations in genes involved in DNA damage repair are common features of upper gastrointestinal malignancies. Genes encoding for proteins important for mismatch, base-excision, and homologous recombination (HR) repair are affected in subsets of these tumors. For example, mutations in *BRCA1/2* were found in about 15% of gastric cancer, loss of *BRCA1* protein expression was found in 21% of gastric cancers and was associated with diffuse-type histology and poor survival. PARP1 (polyADP ribose polymerase 1), a key enzyme involved in base-excision repair may compensate for deficient HR repair resulting from mutations in *BRCA1/2*. In agreement with this observation, clinical activity of single agent PARP inhibitors has been observed in patients with germ-line *BRCA1/2* mutations as well as tumors displaying “*BRCA*ness”, which is characterized by genomic instability and susceptibility to PARP inhibitors in the absence of *BRCA1/2* mutations. Mutations conferring *BRCA*ness have been identified in a number of genes involved in the DNA damage response, including *RAD51C*, *ATM*, *ATR*, *MDC1*, *MRE11A*, *PALB2*, *CHK1/2*, *RAD50*, and components of the Fanconi’s anemia repair pathway but the disease-specific relevance of these mutations is not known. Oncogenic signal transduction pathways, such as PI3K as well as RAF-MEK-ERK pathways may be involved in the regulation of the DNA repair machinery.

The purpose of this research is to elucidate a) whether GI malignancies with mutations in genes conferring *BRCA*ness will be sensitive to PARP inhibition, in particular in combination with inhibitors of oncogenic signal transduction pathways (MEK, PI3K, TGFb, WNT, Notch, Hedgehog, JAK-STAT) or with chemotherapy; b) whether mutations conferring *BRCA*ness provoke an immune response that could be enhanced pharmacologically; c) whether there is a DNA signature predictive of PARP inhibitor sensitivity or combinatorial therapies. Addressing these questions will set the stage for development of increasingly efficient treatment strategies for GI cancers involving PARP inhibitors.

2. Keywords.

Gastric cancer, *BRCA*ness, DNA repair, DNA damage, PARP inhibitor, MEK inhibitor.

3. Accomplishments

What were the major goals of the project?

1. PI to seek regulatory approval from DoD HRPO office. (Korn)
2. PI to seek regulatory approval from IACUC and DoD ACURO office. (Janjigian)
3. Define a genomic signature of *BRCA*ness in gastric cancer (Collisson, Ashworth)
4. Regulation of DNA repair activity by signal transduction pathways (Korn, Ashworth, Janjigian, Collisson)

5. Define the T cell receptor diversity of gastric cancer patients (Fong, Janjigian)

What was accomplished under these goals?

Goal 1. Regulatory approval from DoD HRPO

We have submitted required documentation and addressed questions raised by the office. We are awaiting approval.

Goal 2. Regulatory approval from IACUC and DoD

Obtained.

Goal 3. Define genomic signature of BRCAness in gastric cancer

Computational infrastructure has been built to successfully achieve the aims. In the past six months a group from the United Kingdom has published a new algorithm to assess the degree of homologous recombination deficiency present in a given cancer genome (Davies, H et al., Nat. Med. 2017)). We are also gearing up to evaluate an algorithm used to similar ends with the use of whole Exome data (WES) instead of WGS. We have focused our work on building the computational infrastructure to replicate this process on the samples they published. This requires the calculation of trinucleotide repeat assessment (Alexandrov LB & Stratton MR, Curr Opin Genet Dev, 2010), as well as the number of micro homology- based insertion and deletions. We have been able to implement the prior work and is ongoing on establishing the latter step. Furthermore, we have gained access to and are now downloading the ~50 whole genome low pass sequences published by our collaborators (Cancer Genome Atlas Research, Nature, 2014; Camargo MC et al., The Cancer Genome Atlas, Gastric Cancer, 2016). These are used to train and validate algorithms for detecting BRCAneSS. The dataset with which we are working appear in **table 1**.

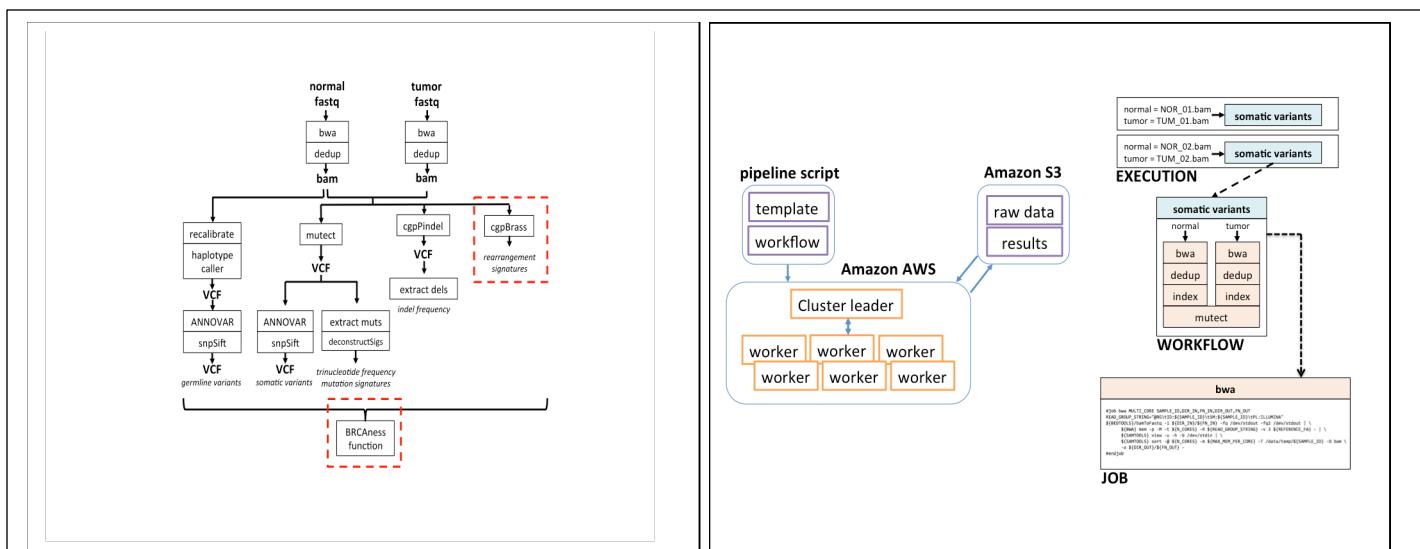


Figure 1. The computational analysis of BRCAness signature from whole genome/exome sequencing. Left panel: BRCAness alignment pipeline (red dashed box indicating work in progress). Right panel: overview of distributed data storage, analysis worker nodes, and example of workflow assessing somatic variants in two paired samples.

Table 1. List of datasets for BRCAneSS signature identification and validation

Data (WGS/WES)	GDC/dbGAP/EGAID	Request	Approval	Analysis
ICGC-Breast cancer	EGAS00001001178	2016-July	2016-November	Test running
TCGA-Gastric cancer	NCI_Genomic Data Commons	2016-August	2016-November	Accessible
Hong Kong-Gastric Cancer	EGAS00001000597	2017-September	Pending	
U-Michigan-multi-Cancer	phs000673.v2.p1	2017-September	Pending	

Goal 4. Investigate regulation of DNA repair activity by signal transduction pathways

We continue to characterize our panel of seven gastric cell lines (MKN7, AGS, KATO-III, NCI-SNU-1, NCI-SNU-5, NCI-SNU16 and NCI-N87) and develop tools to perform screens in these cells.

Major activities:

- Generation of nuclear-tagged versions of gastric lines for drug screens
- Generation of dCas9-KRAB expressing gastric cell lines for CRISPRi screens

Specific Objectives:

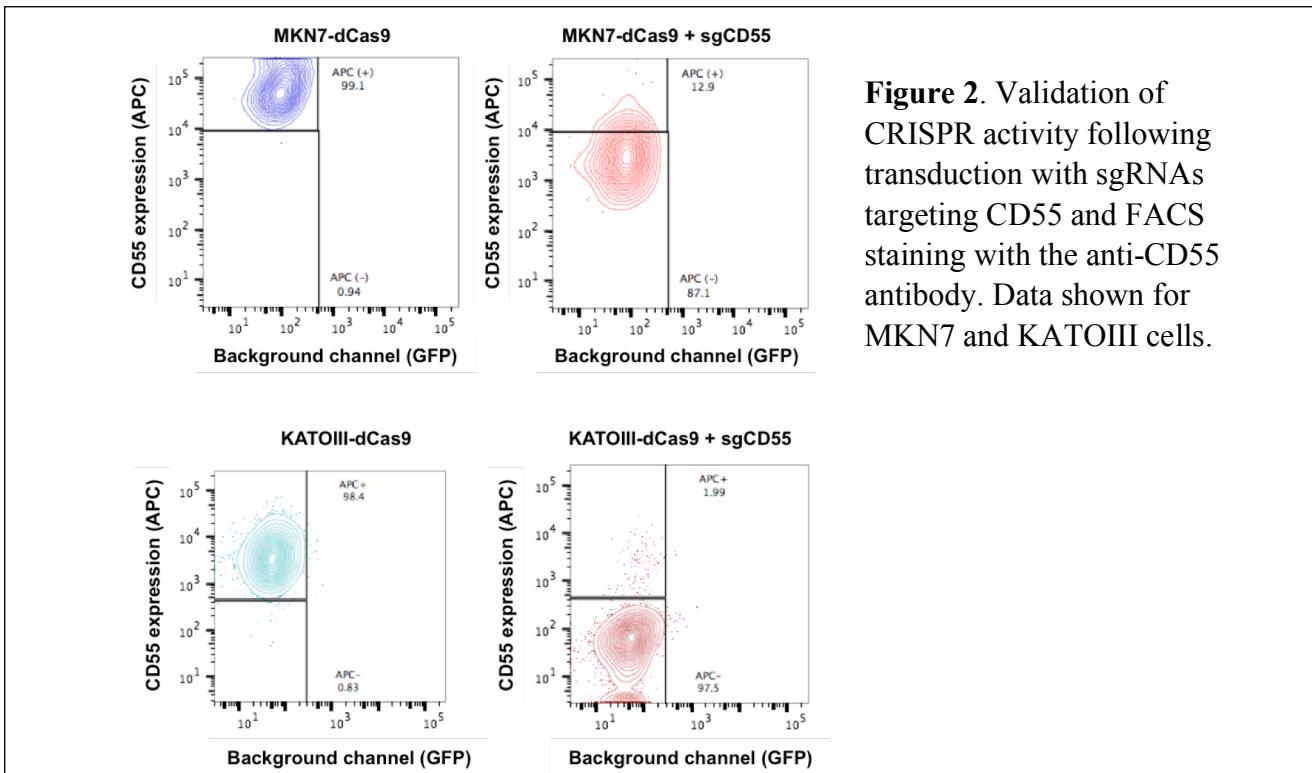
- Assess response of cell lines to treatment with PARP and MEK inhibitors
- Develop screening platform to test genetic vulnerabilities in gastric cancer cell lines
- Identify novel synthetic lethal interactions in gastric cancer that sensitize cells to MEK and PARP inhibitors.

Significant Results/Key Outcomes

We have successfully generated MKN7, AGS, KATO-III, NCI-N87, NCI-SNU-1, NCI-SNU-16 and NCI-N87 cell lines that stably express dCas9-KRAB (Table 2) and have functionally validated five of these cell lines for CRISPRi knockdown. To date, we have confirmed knockdown in the dCas9-expressing AGS, MKN7, KATOIII and NCI-N87 cell lines using an sgRNA targeting CD59 (Figure 2). These validated cell lines will be suitable for large scale CRISPRi pooled sgRNA screening.

Table 2: Phenotypic and genetic characteristics of gastric cancer cell lines studied from our panel, along with whether a stable cell line has been generated

Cell line	Growth type	MSI Status	Tissue	NucLight	dCas9-KRAB	Validated for CRISPRi
AGS	Adherent	Stable	Gastric adenocarcinoma	+	+	+
MKN7	Adherent	Low	Metastatic site; Lymph node	+	+	+
KATO-III	Adherent/ Suspension	Stable	Metastatic site; Pleural effusion	+	+	+
NCI-N87	Adherent	Stable	Metastatic site; Liver	+	+	+
SNU-1	Suspension	High	Gastric carcinoma	+	+	+
SNU-5	Suspension	Stable	Metastatic site; Ascites	+	-	-
SNU-16	Suspension	Stable	Metastatic site; Ascites	+	+	-
HGC-27	Adherent	Stable	Metastatic site; lymph node	-	-	-
Hs746T	Adherent	Stable	Metastatic site left leg muscle	-	-	-
OE19	Adherent	Stable	Oesophagus/ gastric cardia	-	-	-
OE33	Adherent	Stable	Esophageal adenocarcinoma	-	-	-



For our microplate cell line proliferation assays, we have been quantifying cell growth and drug response using the Incucyte high throughput live cell-imaging platform, which reads percent confluence as the output for growth. Because three of the gastric cell lines grow in suspension and some of the adherent lines grow in clumps, we have stably-integrated a nuclear-tagged RFP transgene into these cell lines to more accurately quantify the number of cells in our cell proliferation assays (Table 1 & Figure 2). We have developed a protocol to assess drug response of the suspension lines in a round-bottomed 96 well plate and quantify cell number by total amount of RFP fluorescence (Figure 3). These cell lines and platforms will be useful for validation downstream of the CRISPRi screen.

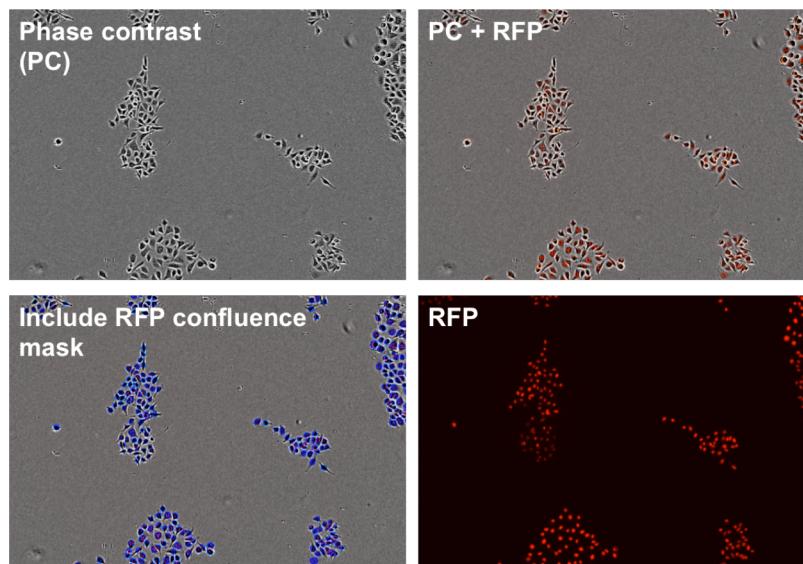


Figure 3: Cells were tagged with a nuclear-tagged RFP transgene to allow quantification of cell number with the Incucyte imaging platform

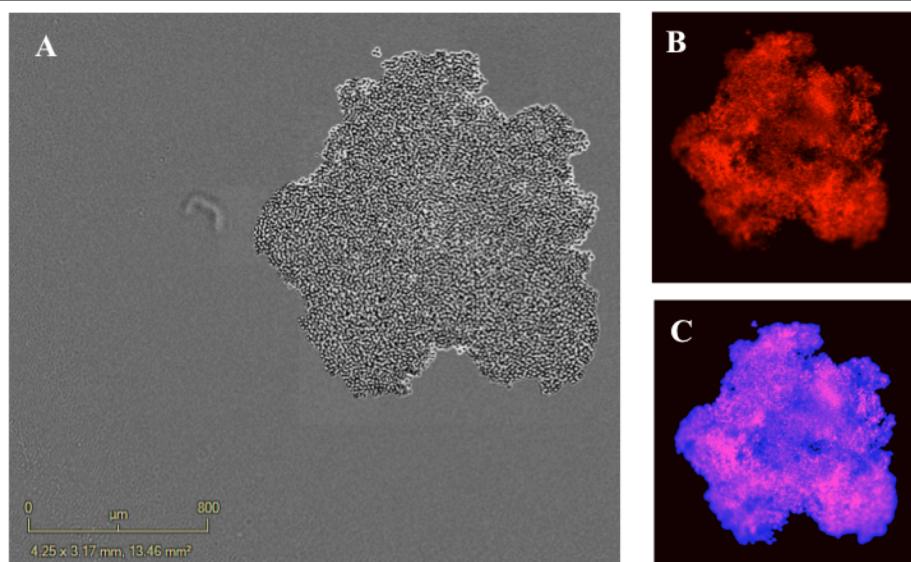
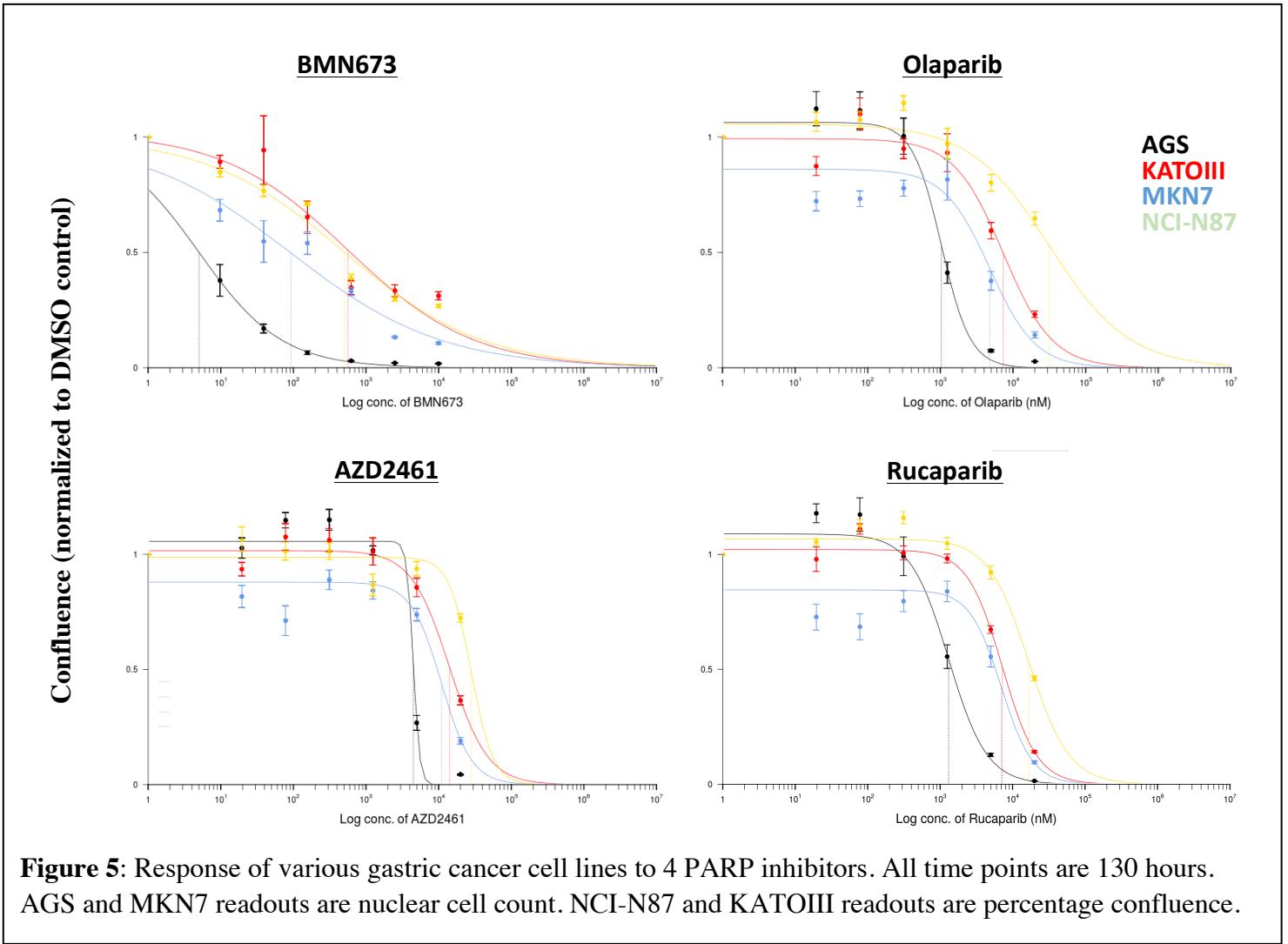


Figure 4: Nuclear-RFP tagged SNU1 cell lines after 6 days in culture. (A) Phase contrast. (B) RFP. (C) Markup image of RFP confluence.

We have initiated drug sensitivity studies and performed dose response experiments in AGS, KATOIII, MKN7 and NCI-N87 cells to determine the drug response for PARP inhibitors. Cells were seeded into 384-well plates and allowed to attach overnight before starting drug treatment. Growth was monitored using the Incucyte Zoom imaging system and assessed 132 hours following the administration of drug, when the untreated fast-growing AGS cells reached confluence.



The AGS cell line was the most sensitive cell line to treatment with all 4 PARP inhibitors (BMN673, Olaparib, AZD2461, Rucaparib), while the KATOIII, MKN7 and NCI-N87 cell lines were markedly resistant to treatment with all four inhibitors.

We also performed drug interaction assay for the combination of the PARP inhibitor Talazoparib (BMN673) with the MEK inhibitor GSK1120212 (trametinib) in a panel of 10 gastric and GE junction adenocarcinoma cell lines (Figure 6). In these experiments, Cell Titer Glo (CTG) assay was used to assess cell viability at 72 hours.

In this assay the shorter time range and the lower single drug concentrations are used as compared to the Incucyte assay, which more thoroughly determines differential cellular response to a single drug. The drug interaction assay determines whether the treatment with two drugs results in a synergism or potentiation of the effects of each of the drugs alone.

The cell lines differed in their response to a combination of Talazoparib GSK1120212: a subset of cells displayed a synergism, while the other cell lines were not more sensitive to one or both compounds when they were used in a combination. (Figure 6 A, B, C)

Figure 6: Effects of MEK and/or PARP inhibition on cell viability in gastric cancer cell lines, demonstrating drug synergy (A) or lack of synergy (B) or the resistance to one or to both MEKi and PARPi (C).

A. Cells displaying synergistic or additive response to MEKi+PARPi combination: SNU-16, SNU-1, AGS, OE19;

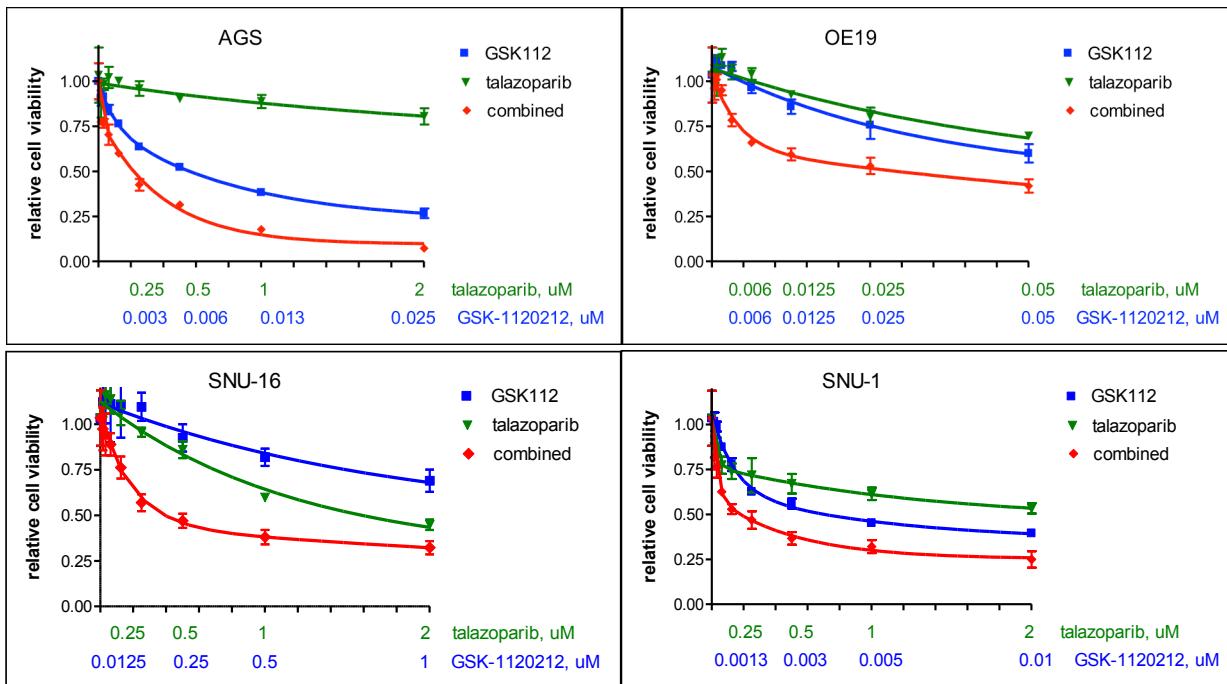


Figure 6B. Cells displaying sensitivity to each of MEKi or PARPi alone, but no synergistic response to their combination: OE-33, NCI-N87;

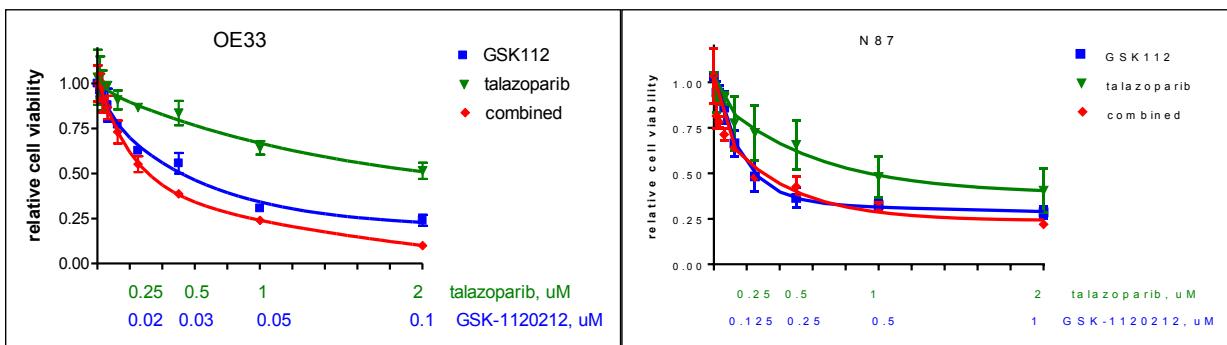
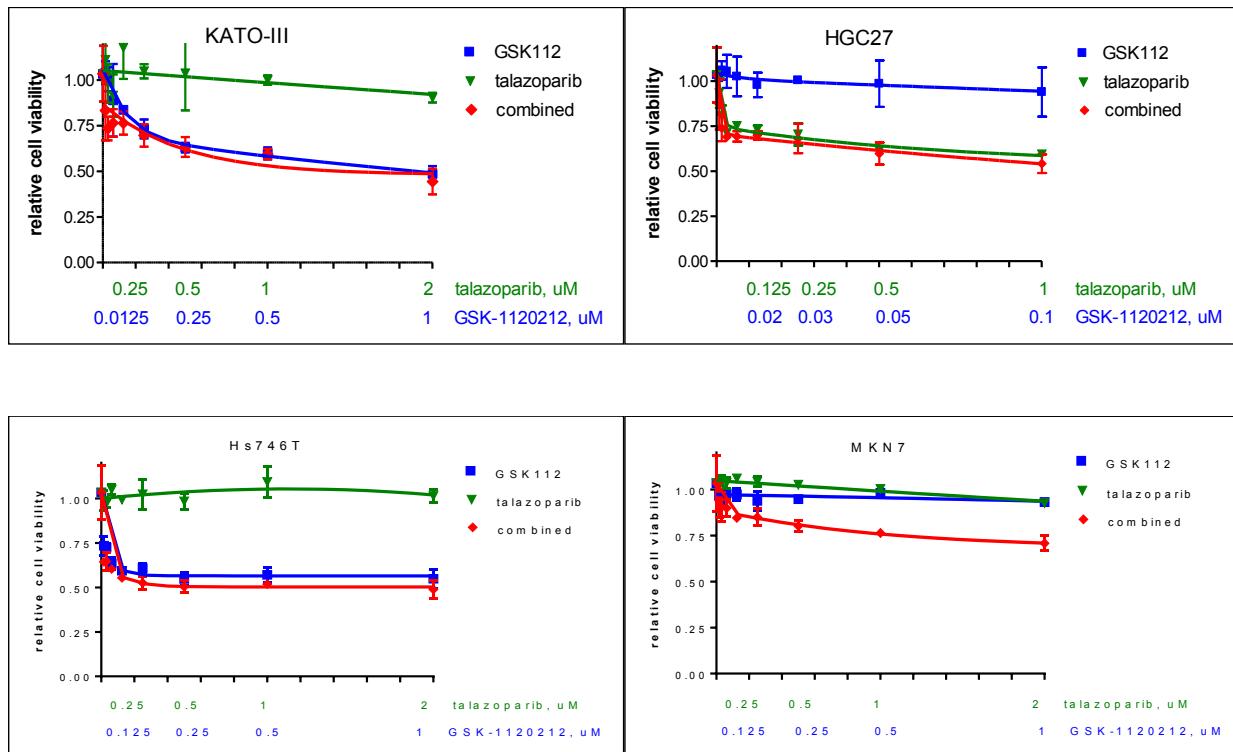


Figure 6C. Cells displaying sensitivity to one or to none of MEKi or PARPi, and no synergistic response to their combination: KATO-III, HGC27, Hs746T, MKN7;



We have screened cell line databases (<http://www.broadinstitute.org/cCLE>) and found the BRCAness genes aberrations for several of these gastro-esophageal cell lines (Table 3). A wide spectrum of activity of individual drugs and their combination was seen and synergistic responses did not correlate with known defects in DNA repair genes. However, the pathogenicity of BRCA1 mutations in MKN7 and Hs746 is unknown and under investigation.

Table 3: Summary of gastro-esophageal cell lines' BRCAness gene aberrations, as well as the cells' sensitivity and synergistic response to MEKi and PARPi (as determined by drug interaction assay CTG).

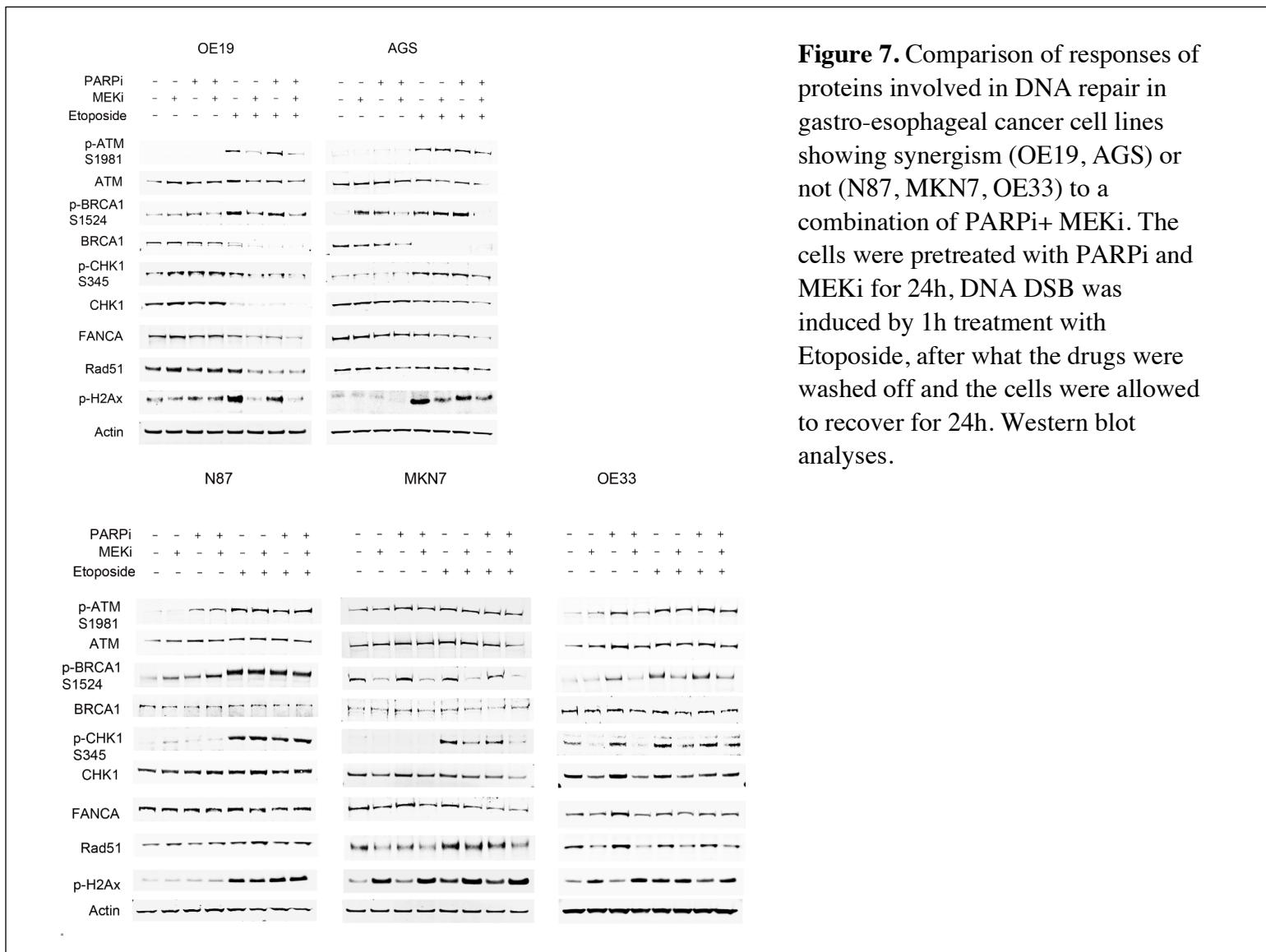
Cell line name	Cell line description	BRCAness gene aberration	Sensitivity to MEKi GSK1120212, IC50, uM	Sensitivity to PARPi BMN673, IC50, uM	Synergism MEKi+ PARPi
AGS	Gastric adenocarcinoma	none	0.004	> 5	+
MKN7	Gastric well differentiated tubular adenocarcinoma	BRCA1 (pathogenicity unknown)	>10	>5	-
KATO-III	Gastric adenocarcinoma derived from metastatic site (pleural effusion and supraclavicular and axillary lymph nodes and Douglas cul-de-sac)	ATM (pathogenicity unknown) ATR (pathogenicity unknown) BLM (pathogenicity unknown)	0.7	>5	-
NCI-	Gastric carcinoma derived	CDK12 ampl	0.32	3.47	-

N87	from metastatic site (liver)	NBN ampl MSH6 missense			
SNU-1	Gastric undifferentiated adenocarcinoma	ATM FS insertion BLM FS deletion BRCA2 FS deletion BRCA2 (pathogenicity unknown) BRCA1 (pathogenicity unknown) PARP1 (pathogenicity unknown) MLH1 Nonsense ARID1A FS missense	0.003	2.8	+++
SNU-16	Gastric undifferentiated adenocarcinoma derived from metastatic site (ascites)	none	0.53	1.8	+++
HGC- 27	Gastric undifferentiated adenocarcinoma derived from metastatic site (lymph node)	CDK12 nonsense FANCA FS missense ATM (pathogenicity unknown) ATR (pathogenicity unknown) BRCA2 (pathogenicity unknown) RAD50 (pathogenicity unknown)	>10	3.4	-
Hs746T	Gastric adenocarcinoma derived from metastatic site (left leg muscle)	BRCA1 (pathogenicity unknown)	0.2	> 5	-
OE19	Adenocarcinoma of gastric cardiac/oesophageal gastric junction	NBN ampl	0.02	0.22	+++
OE33	Adenocarcinoma of the lower oesophagus	BLM (pathogenicity unknown) CDK12 (pathogenicity unknown)	0.03	2	-

To better understand the underlying mechanisms conferring sensitivity to drug combinations, we are investigating the biochemical response of each cell line to drug treatments by Western blot.

As shown in Figure 6, cell lines demonstrating synergistic cell growth inhibition following treatment with MEK and PARP inhibitor showed a different molecular response to DNA damage than those cell lines not responding synergistically. In particular, synergistic cells displayed reduced levels of total BRCA1 and CHK1 after treatment with the DNA damaging agent Etoposide. Non-synergistic cells activated DNA damage response (p-ATM and p-H2Ax) in response to MEKi or PARPi in the absence of Etoposide (as opposed to the synergistic gastric cancer cell lines OE19 and AGS).

In synergistic cells the pretreatment with MEKi or with drug combination results in reduced levels of p-ATM and p-H2Ax activated by DNA damage. Reduced phosphorylation of ATM and H2AX, as well as decreased expression of FANCA, were key findings shared by all synergistic cell lines. In non-synergistic cells pretreated with MEKi, pH2Ax levels remained activated in response to Etoposide. These observations suggest that the MEK inhibitor or its combination with PARP inhibition impairs the ability of cells either to activate DNA damage signaling or to repair DNA double-strand breaks by homologous recombination.



We will focus our subsequent work on the mechanism of DNA damage response in the different subtypes of gastric cancer cell lines (synergistic or not) and on the MEKi effect on DNA damage signaling and repair.

Goal 5. Define the T cell receptor diversity of gastric cancer patients

Samples collection will commence once the clinical trial of olaparib and the VEGFR antagonist, ramucirumab, opens. Batch analysis will be performed once sufficient number of tissue samples is available.

Conclusions

1. The gastric cancer cells demonstrated differential response to a combination of MEKi+ PARPi: varying from synergy to resistance to one or to both compounds.
2. The synergistic response did not correlate with known aberrations of BRCAness genes.
3. The synergistic response correlated with the ability of cells to activate DNA damage response. The underlying mechanism of DNA damage signaling is under further study.

Other Achievements

Nothing to report.

Protocol and Activity Status (if applicable).

(a) Human Use Regulatory Protocols

TOTAL PROTOCOLS: 2

1. Molecular Profiling in Gastrointestinal Malignancies (UCSF IRB#: 13-12574). Status: active, expiration date 12/4/17

2. A Phase 1 / 2 Study of Olaparib in Combination with Ramucirumab in Metastatic Gastric and Gastroesophageal Junction Adenocarcinoma (10017760). Status: Under IRB review (NCI)

(b) Use of Human Cadavers for Research Development Test & Evaluation (RDT&E), Education or Training

No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).

(c) Animal Use Regulatory Protocols

TOTAL PROTOCOL(S): 1

Title: Cell Cultures and Xenografts from Esophagogastric, Pancreatic, Colorectal and Neuroendocrine Tumors, IACUC protocol number 10-02-003, Protocol Principal Investigator Yelena Janjigian

Target required for statistical significance: 760

Target approved for statistical significance: 760

Submitted to and Approved by:

-This protocol was approved by the Memorial Sloan-Kettering Cancer Center, New York IACUC on 17-MAR-2016.

-Approved by the USAMRMC Animal Care and Use Review Office (ACURO) as of 03-AUG-2016

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals and objectives?

We will complete downloading the 50 whole genome sequences described above. Once this is achieved and the analytical pipeline described above is fully functional, initial test runs will be performed.

The dCas9-expressing cell lines are now ready to be used in a CRISPRi-based screen. Our initial screen will be a dropout screen assessing sensitivity of the MKN7 cells to the PARP inhibitor, olaparib, the ATR inhibitor, AZD6738. Both MKN7 and KATOIII cell lines displayed resistance to both compounds, so would be solid candidates for this screen. We have decided to move forward with MKN7 cells because the KATOIII cell line harbors mutation in ATM, ATR and CDH1, all putative drivers of gastric cancer. Although MKN7 cells have a missense mutation in BRCA1, it is believed to be non-pathogenic. The pooled CRISPRi screen will be carried out with a 5000-gene library (kinase, phosphatases & cancer-associated genes). The drug will be replaced every 3-4 days and the experiment will last for 3 weeks.

As part of our effort to further understand the mechanism underlying MEK and PARP synergism, we will continue to study DNA-repair activity in selected gastric cell lines. We will employ a homologous recombination reporter assay that utilizes a DR-GFP reporter plasmid and I-SceI endonuclease (Pierce et al., Genes Dev, 1999). We have already obtained a control cell line based on U2OS cells and obtained and purified

plasmids: pDRGFP, pimEJ5GFP, pCAG-DsRed2, pCBASceI which will be used for the assay. We are in process of transfection optimization of gastric cell lines with these plasmids and the selection of stable clones expressing pDRGFP (Homologues recombination reporter) and pimEJ5GFP (Non-homologues end-joining reporter). Furthermore, we have started to systematically assess changes in cell cycle distribution following etoposide, MEK and PARP inhibitor treatments to distinguish changes in protein expression resulting from cell cycle arrests from direct, inhibitor-dependent effects.

4. IMPACT.

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Nothing to report.

6. PRODUCTS.

Nothing to report.

Participants & Other Collaborating Organizations

Individual	Role	Affiliation	Credentials	Responsibilities
Eric Collisson	PI	UCSF	M.D.	Oversight, project planning and reporting
David Quigley	Computational Biologist	UCSF	PH.D.	Data analysis and reporting
Wei Wu	Analyst	UCSF	PH.D.	Data generation, reporting
Lawrence Fong	PI	UCSF	M.D., PH.D.	Oversight, project planning and reporting
Alan Ashworth	PI	UCSF	PH.D.	Oversight, project planning and reporting
Patrick O'Leary	Postdoctoral Fellow	UCSF	PH.D.	Design, execution, and interpretation of CRISPR experiments
Morgan Diolaiti	Specialist	UCSF	PH.D.	Experimental planning and reporting
Jefferson Woods	SRA	UCSF	B.S.	Perform drug screens and CRISPR experiments
Janjigian, Yelena	PI	MSKCC	M.D.	Oversight, project planning and reporting
Yaelle Tuvy	Research study assistant	MSKCC	B.S.	Coordination of tissue acquisition
Efsevia Vakiani	Pathologist	MSKCC	M.D.	Assessment of tissue samples
W. Michael Korn	PI	UCSF	M.D.	Overall project coordination, oversight, project planning and reporting
Olga Mirzoeva	Scientist	UCSF	PH.D.	Planning and execution of cell line experiments, data aggregation and reporting

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. W. Michael Korn, one of the key PIs, has stepped down from his role effective 8/31/2017. Dr. E. Collisson will be taking over the overall project coordination. Dr. Olga Mirzoeva will be moving to Dr. Collisson's laboratory effective October 24th. Dr. Korn's laboratory and equipment will be closed and partially moved to Dr. Collisson's laboratory at a different campus of UCSF. We anticipate a delay in the continuous experimental progress due to the move.

Changes/Problems:

a. Anticipated Problems/Issues

Delay due to personnel reorganization and moving. Specifically, Dr. Korn has accepted employment elsewhere and Dr. Collisson is slowly ramping up management and supervisory duties. We anticipate this process being complete December 1, 2017 although additional delays may be unavoidable.

Special Reporting Requirements:

Quad Charts: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.